What's Next for Cancer Immunotherapy?

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Bernard A. Fox, PhD – COI Disclosures

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Immunotherapy can Cure Patients of Their Cancer!

Immunotherapy can Cure Patients of Their Cancer!

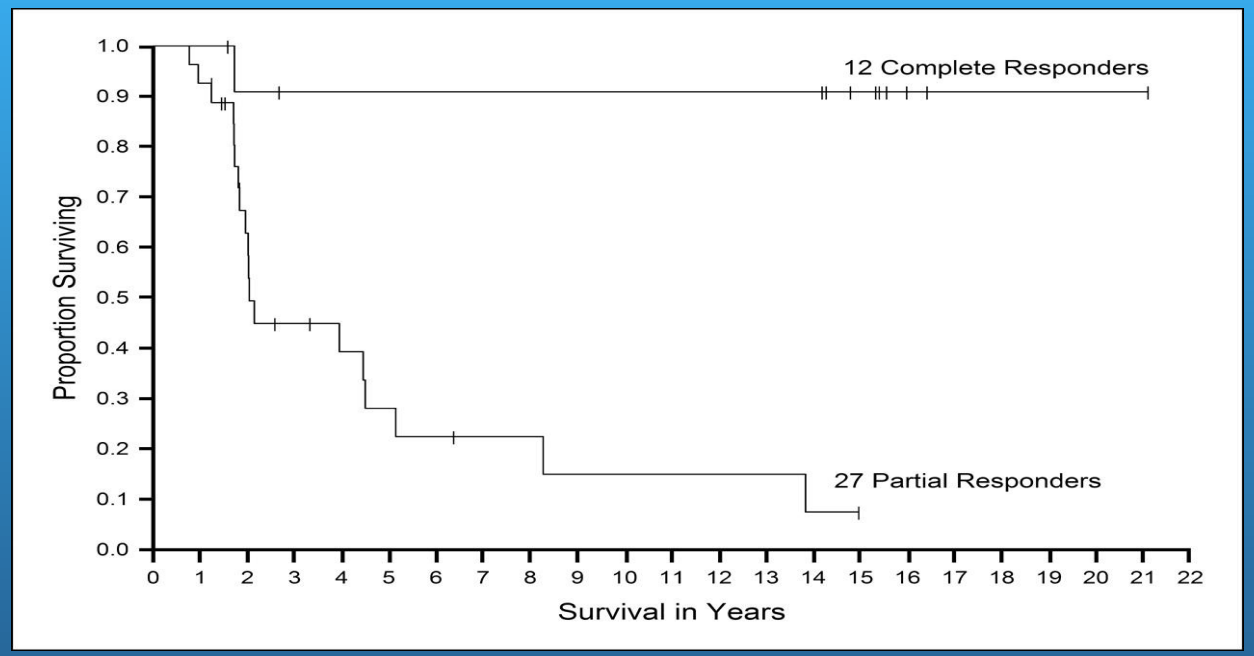
Cure... Yeah, we said it!

Get your SITC "Cure" t-shirt at the Registration Desk for only $25 each
All proceeds support SITC's Forward Fund
Take a photo of you in your t-shirt and you could be featured on the SITC website!
Visit **www.sitcancer.org/support/forwardfund** for more information

Engage . . . Collaborate . . . Learn

Immunotherapy can Cure Patients of Their Cancer!

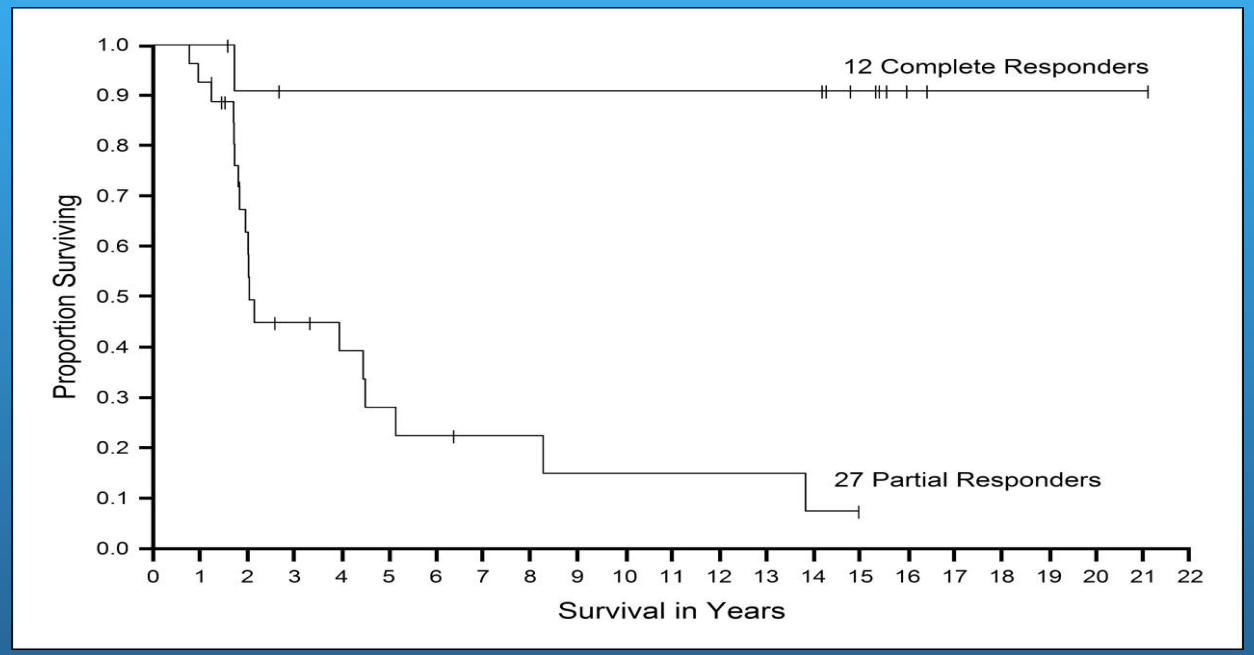
- Certainly IL-2 can



Smith F O et al. Clin Cancer Res 2008;14:5610-5618

Immunotherapy can Cure Patients of Their Cancer!

- Certainly IL-2 can



Smith F O et al. Clin Cancer Res 2008;14:5610-5618

- Does anti-PD-1 give us the same result? Too early to say?

What is different about IL-2?

What is different about IL-2?

I think it was the 1st "Combination" Immunotherapy?

Growth factor for T cells and NK cells..

But it induced cytokine storm…

That cytokine storm "impacted":

APCs, B cells, innate immunity & Tu

FUTURE:

More Combinations of Standard Cancer Therapies with Immunotherapy

Expect that these will get “smarter”

Objectives: FDA Workshop on Immune-Oncology Combos

1. To identify best practices regarding patient selection for immune-oncology combinations –*Multiplex/TMB/GEP/PD-L1*
2. To identify best practices regarding dose selection and optimization for IO combinations – *Data to suggest schedule may be important*
3. To discuss the utility of biomarkers as pharmacodynamics endpoints to aid in dose optimization.
4. To discuss how the expectation of the demonstration of the contribution of each agent has to a combination and strategies to isolate the effect of each individual agent –

https://www.fda.gov/Drugs/NewsEvents/ucm562746.htm

REVIEW Open Access

Novel technologies and emerging biomarkers for personalized cancer immunotherapy

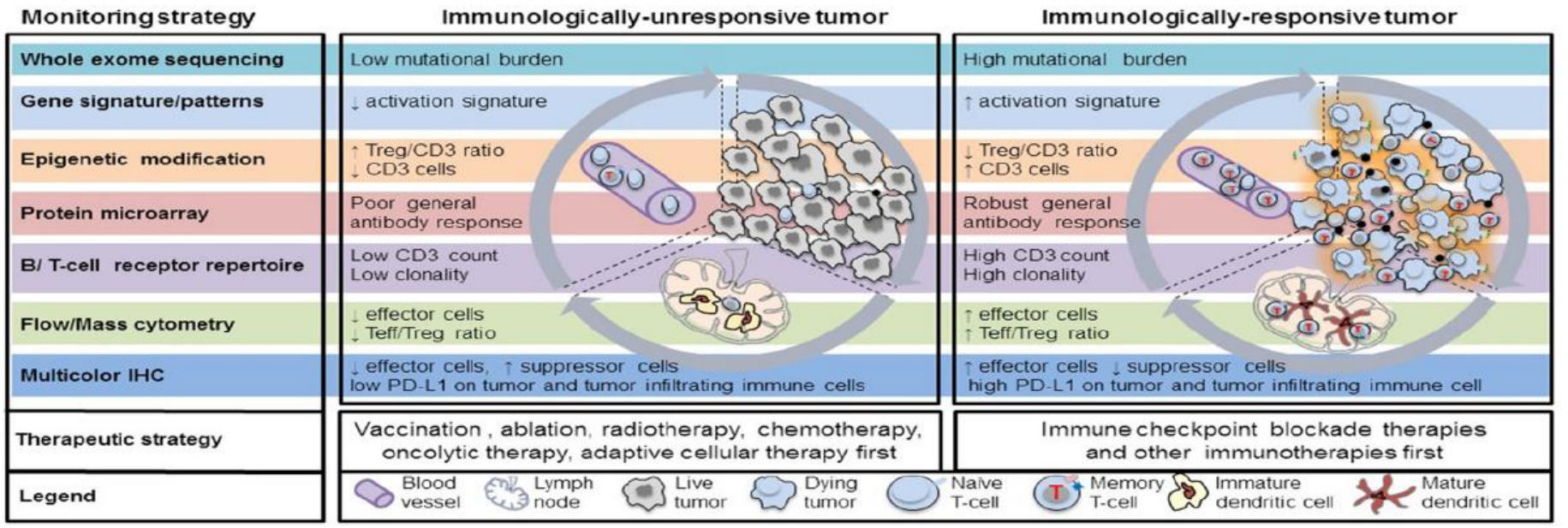
Journal for ImmunoTherapy of Cancer

Yuan *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:3
DOI 10.1186/s40425-016-0107-3

Jianda Yuan[1*], Priti S. Hegde[2], Raphael Clynes[3], Periklis G. Foukas[4,5], Alexandre Harari[4], Thomas O. Kleen[6], Pia Kvistborg[7], Cristina Maccalli[8], Holden T. Maecker[9], David B. Page[10], Harlan Robins[11], Wenru Song[12], Edward C. Stack[13], Ena Wang[14], Theresa L. Whiteside[15], Yingdong Zhao[16], Heinz Zwierzina[17], Lisa H. Butterfield[18] and Bernard A. Fox[10*]

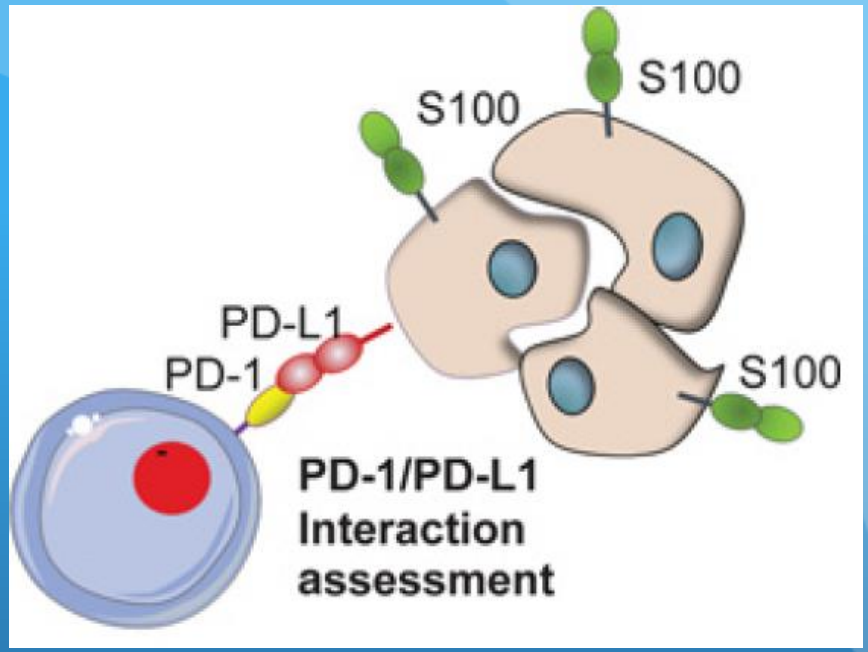
SITC Immune Biomarkers Task Force

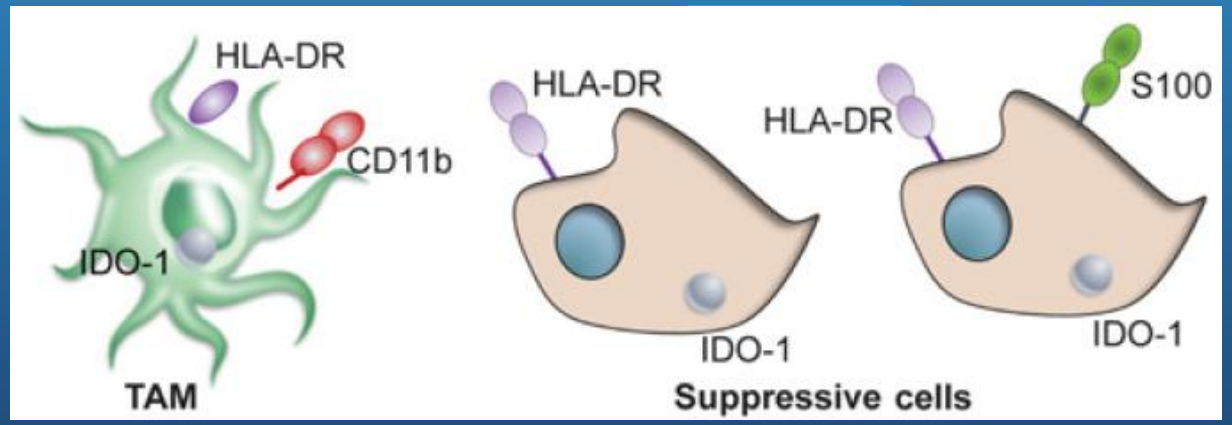
Novel immune monitoring assays for biomarker discovery and personalized cancer immunotherapy

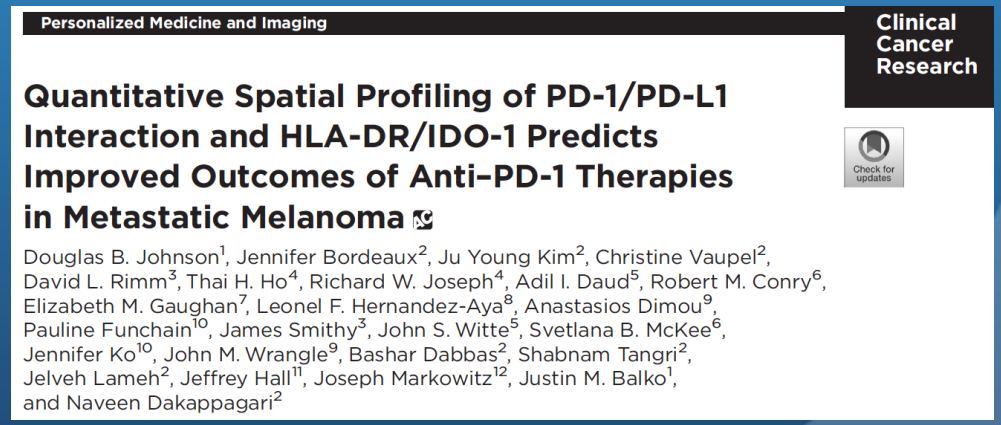


What Do We Know in 2019?

- PD-L1+ tumors have better RR
- PD-1 and PD-L1 (proximity) do better
- IDO and HLA-DR (proximity) do better (upregulated by IFN-γ / surrogate)






Personalized Medicine and Imaging

Clinical Cancer Research

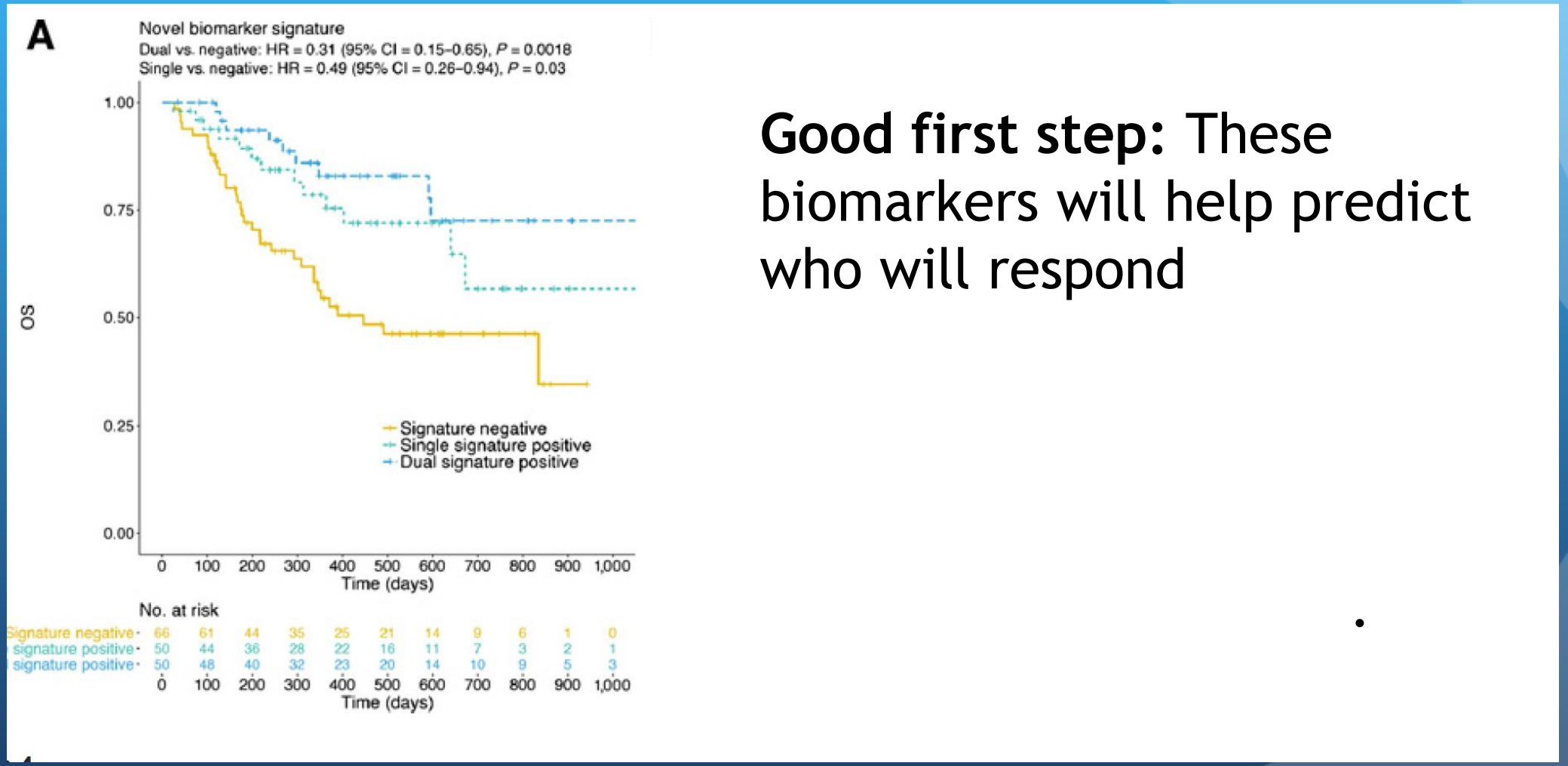
Quantitative Spatial Profiling of PD-1/PD-L1 Interaction and HLA-DR/IDO-1 Predicts Improved Outcomes of Anti–PD-1 Therapies in Metastatic Melanoma

Douglas B. Johnson[1], Jennifer Bordeaux[2], Ju Young Kim[2], Christine Vaupel[2], David L. Rimm[3], Thai H. Ho[4], Richard W. Joseph[4], Adil I. Daud[5], Robert M. Conry[6], Elizabeth M. Gaughan[7], Leonel F. Hernandez-Aya[8], Anastasios Dimou[9], Pauline Funchain[10], James Smithy[3], John S. Witte[5], Svetlana B. McKee[6], Jennifer Ko[10], John M. Wrangle[9], Bashar Dabbas[2], Shabnam Tangri[2], Jelveh Lameh[2], Jeffrey Hall[11], Joseph Markowitz[12], Justin M. Balko[1], and Naveen Dakappagari[2]

Clin Cancer Res. 2018 Nov 1;24(21):5250-5260

Earle A. Chiles Research Institute

IDO/HLA-DR and PD-1/PD-L1 Interaction Tests Predict OS Predictive Biomarkers for response to anti-PD-1



Good first step: These biomarkers will help predict who will respond

Clin Cancer Res. 2018 Nov 1;24(21):5250-5260

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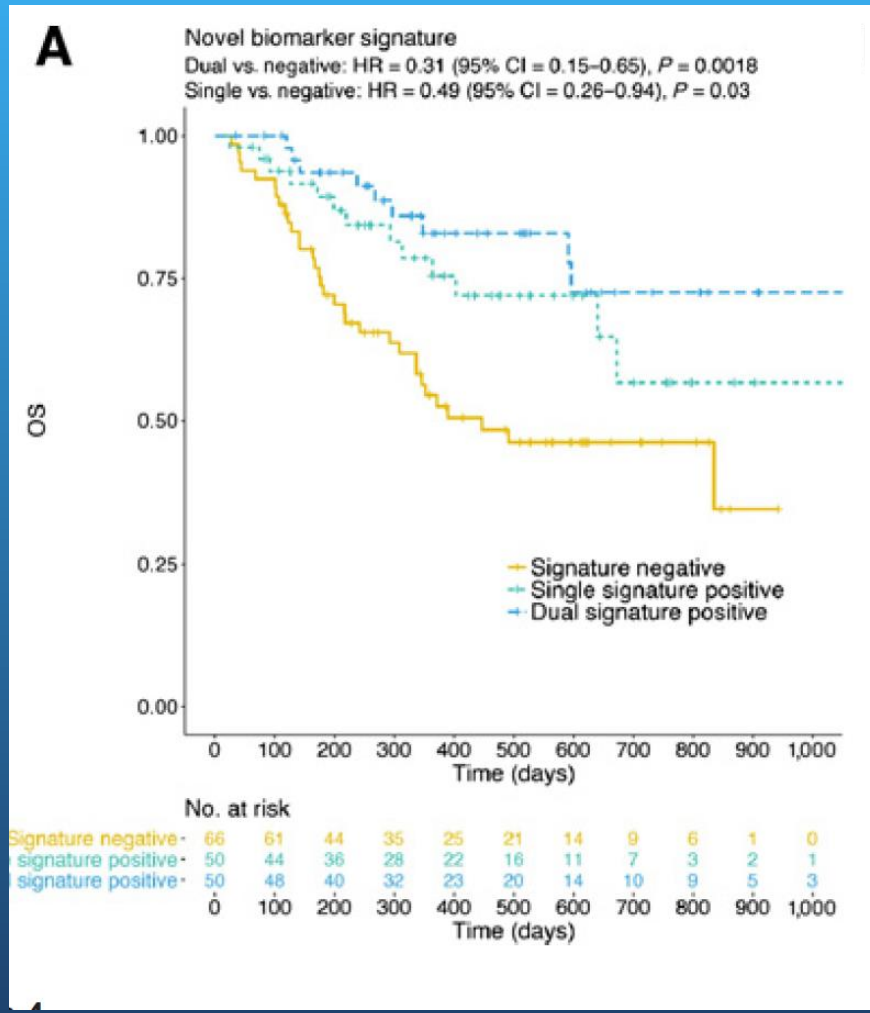
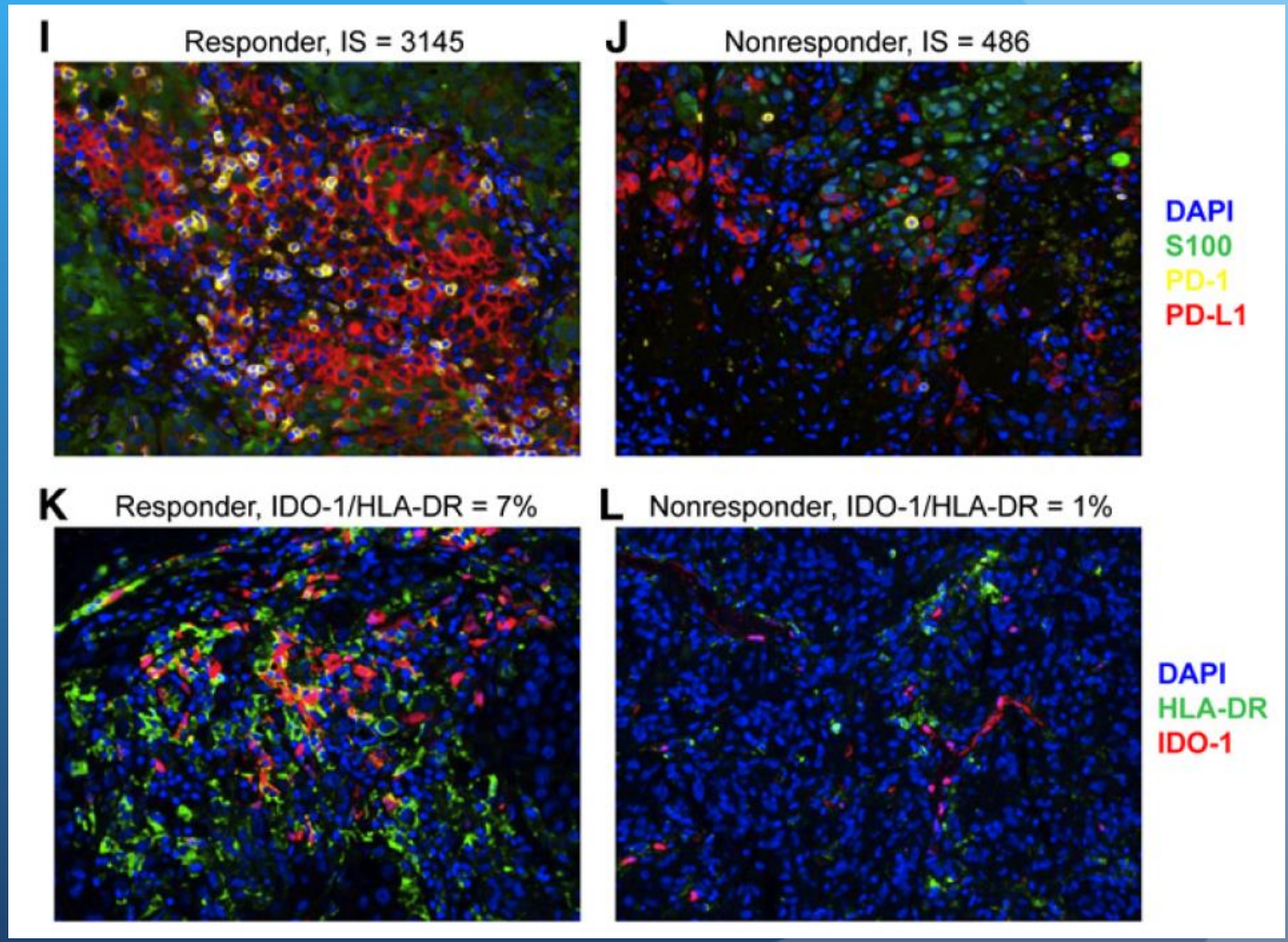


Good first step: These biomarkers will help predict who will respond

Next step: Biomarkers that will identify what treatment a non-responder needs to make them a responder.

Clin Cancer Res. 2018 Nov 1;24(21):5250-5260

How Will We Identify New "Predictive" Biomarkers To Tailor The Next Generation of Immunotherapy?

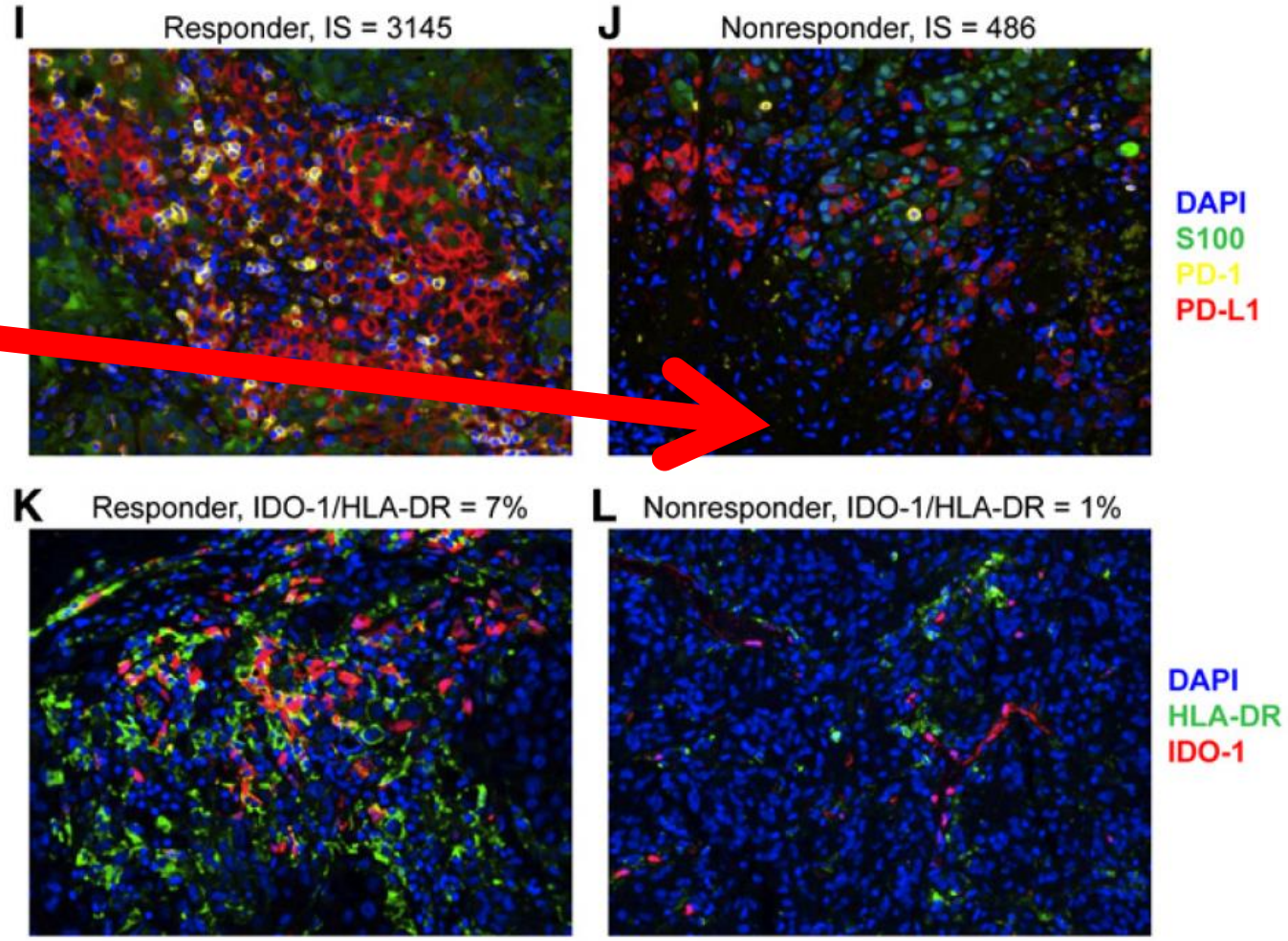


Clin Cancer Res. 2018 Nov 1;24(21):5250-5260

How Will We Identify New "Predictive" Biomarkers To Tailor The Next Generation of Immunotherapy?

How will we figure out what is going on here?

Standard GEP looks at dissected tissue but not a "small" region of interest

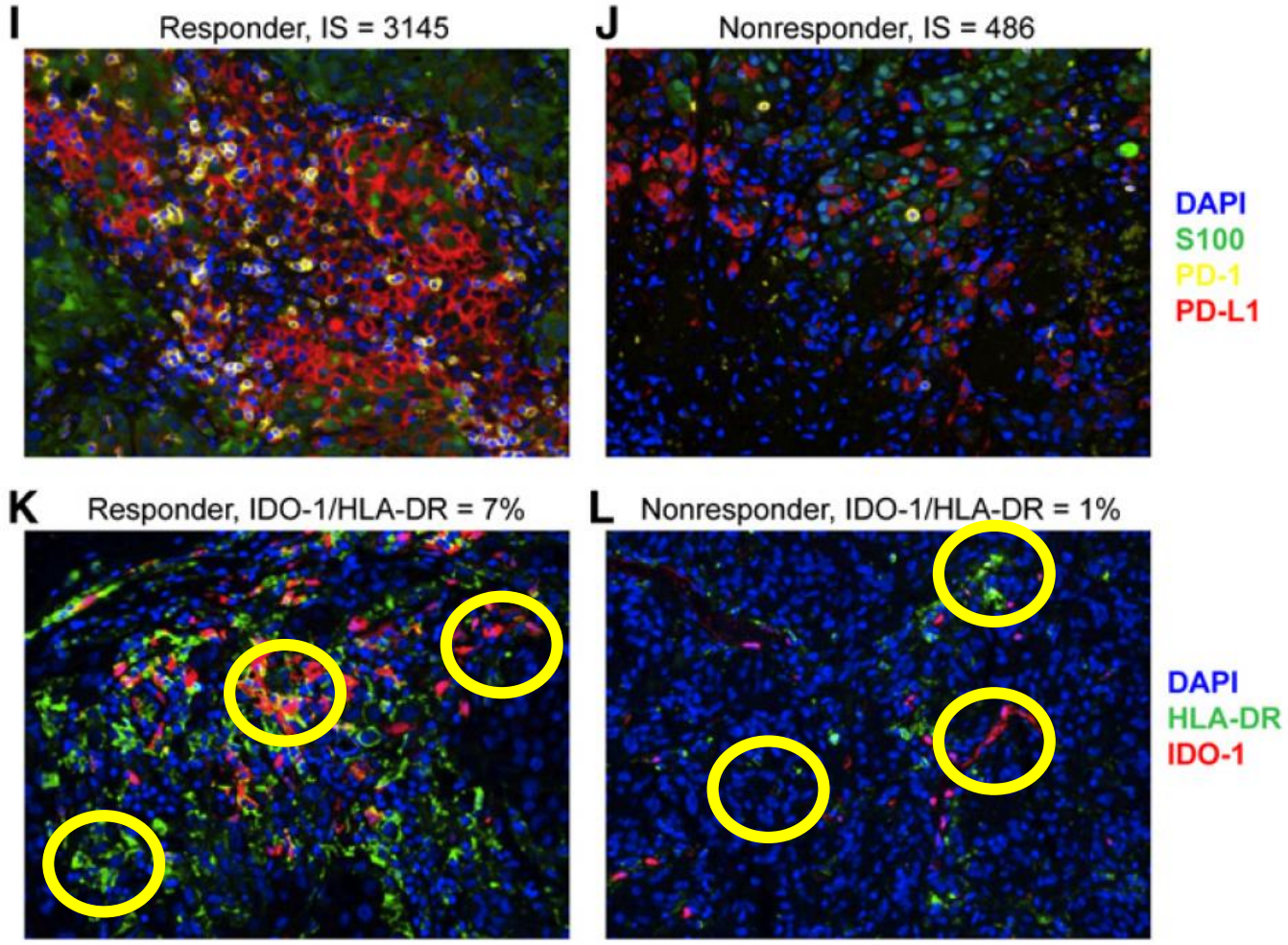


Clin Cancer Res. 2018 Nov 1;24(21):5250-5260

How Will We Identify New "Predictive" Biomarkers To Tailor The Next Generation of Immunotherapy?

New Technology:

Digital Spatial Profiling
Let's us look at small areas – single cells to 300 micron circles
- 40+ Abs
- 1600+ RNA transcripts

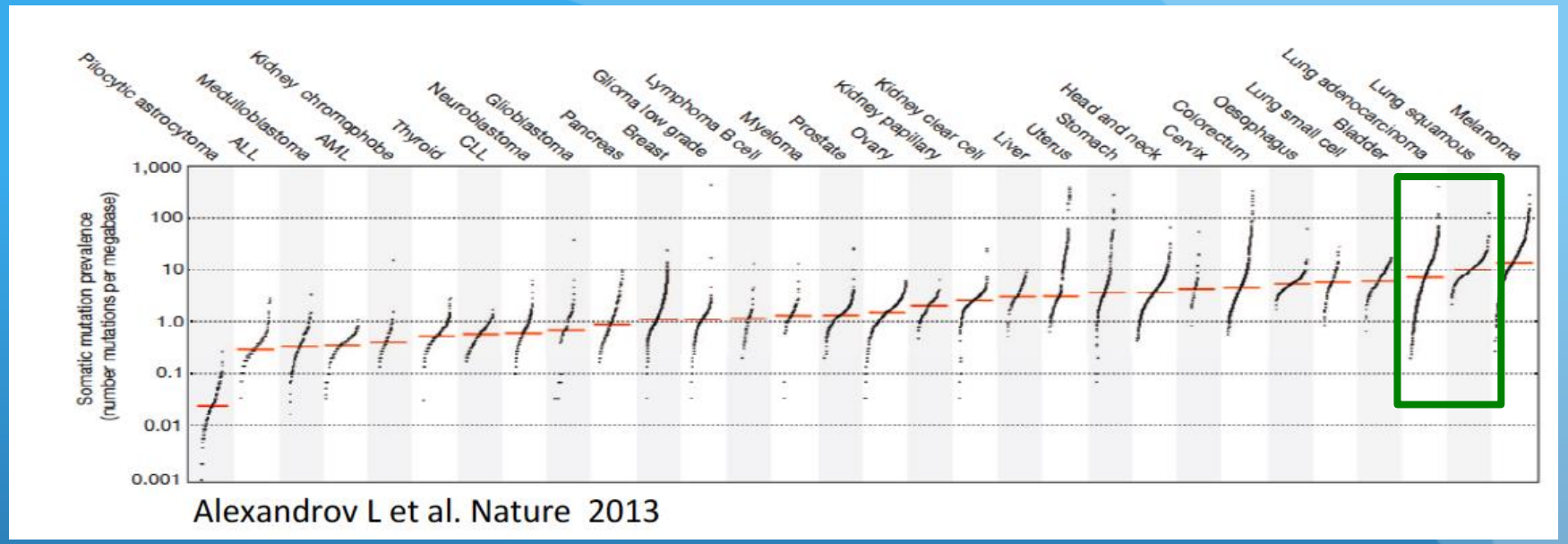


Clin Cancer Res. 2018 Nov 1;24(21):5250-5260

TMB Hi do better!

Tumor mutational burden (TMB) is variable.

Less than 50% of Tu are Hi TMB



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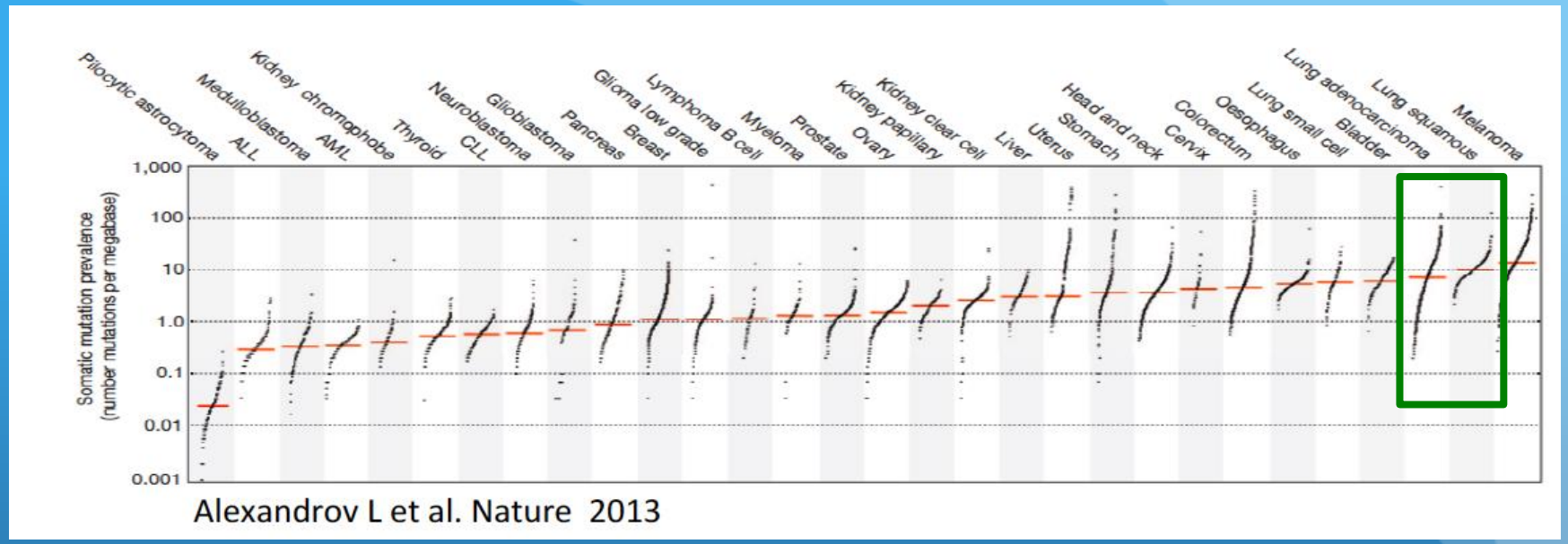
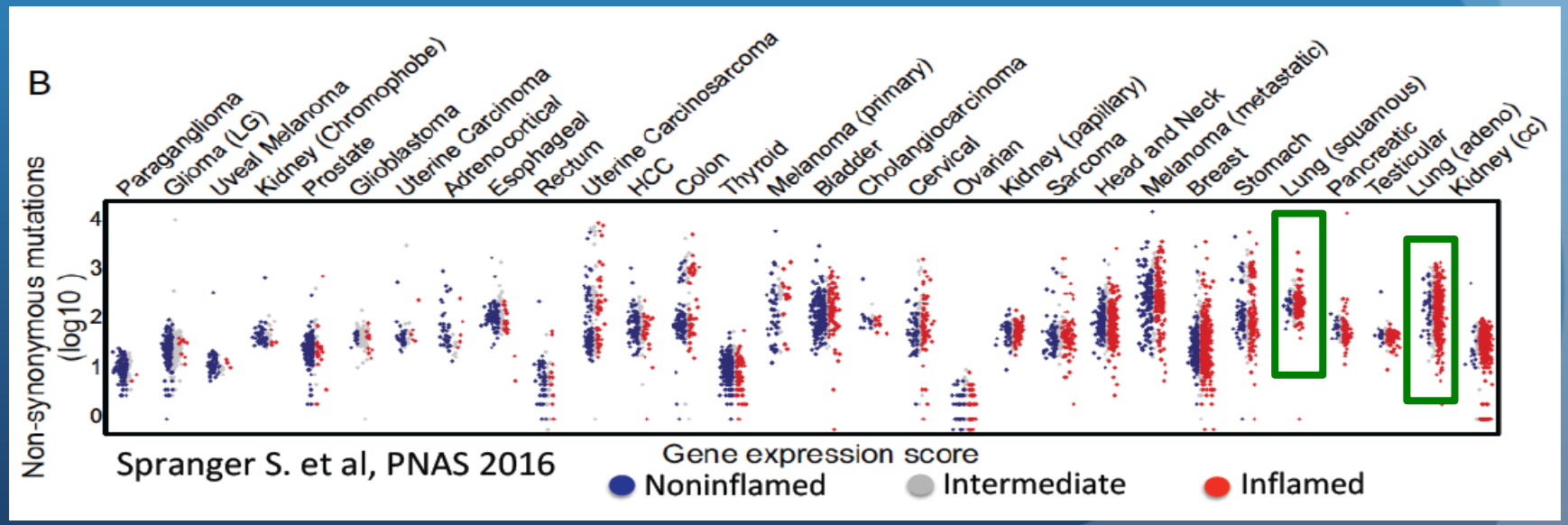


Alexandrov L et al. Nature 2013



Spranger S. et al, PNAS 2016

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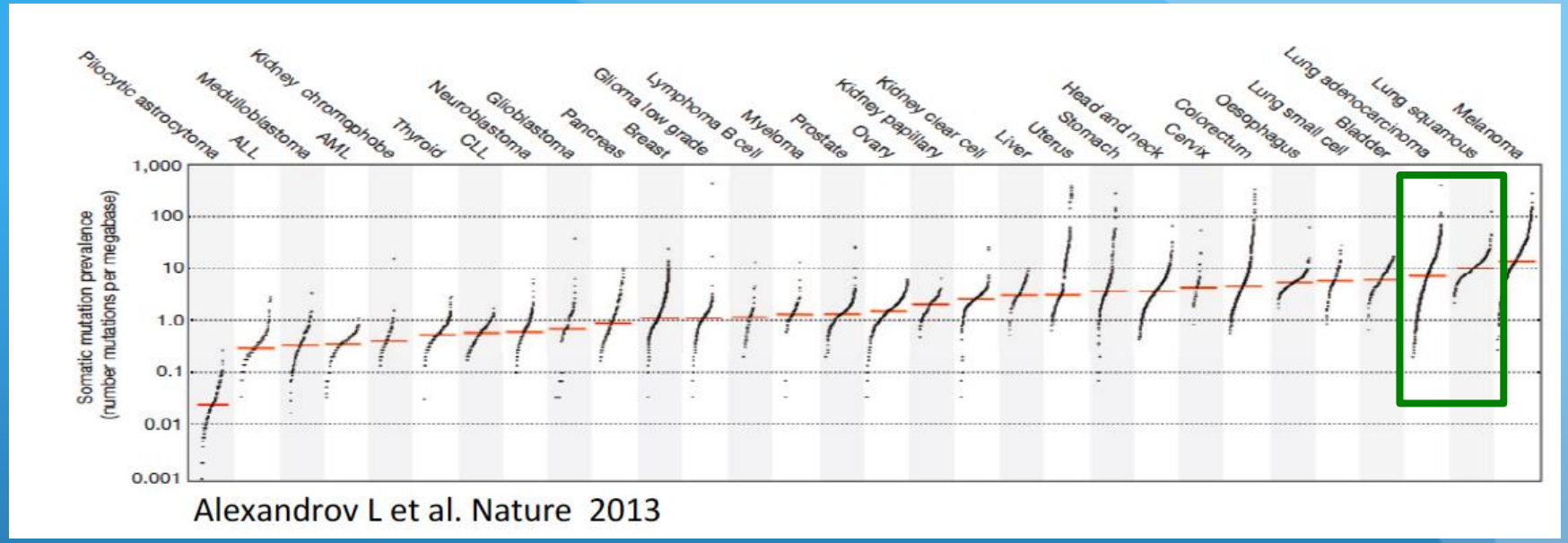
NEED TO INDUCE/ BOOST IMMUNITY



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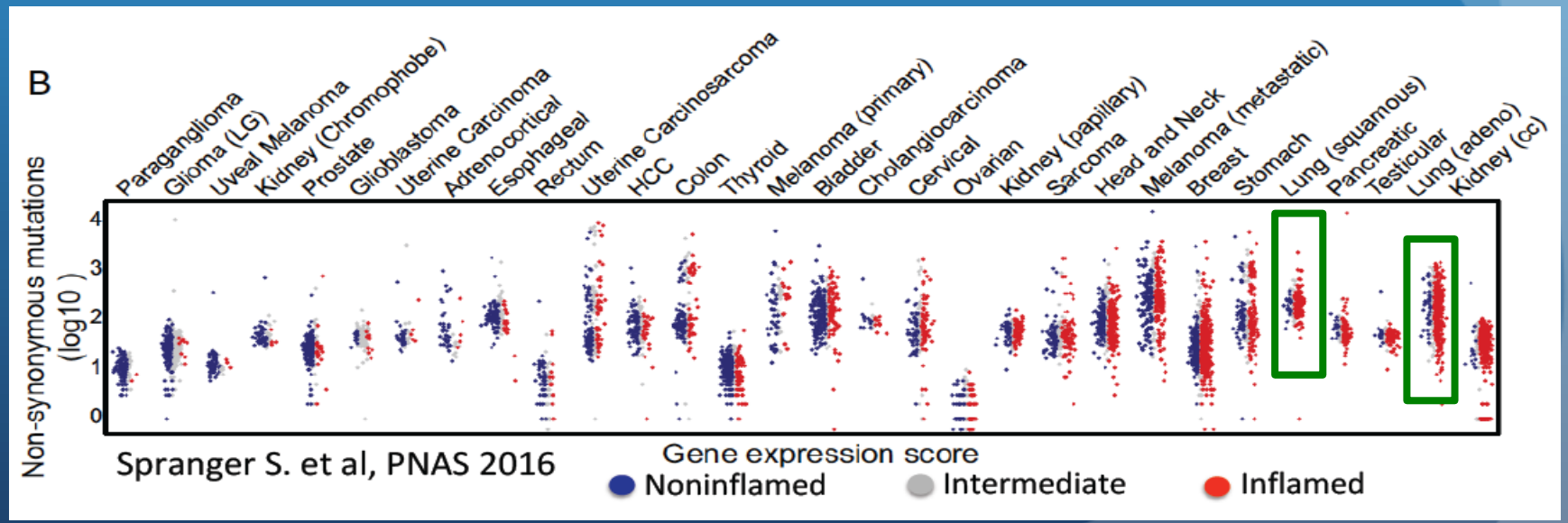

Spranger S. et al, PNAS 2016

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How to Induce or Boost Anticancer Immunity?

- Chemotherapy?
- Cytokines?
- Intratumoral Treatments? / Adjuvants?
- Radiation?
- Vaccines?
- Viruses?

How to Induce or Boost Anticancer Immunity?

- Chemotherapy?
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- Radiat
- Vaccine
- Viruses?

Potentially all of these strategies DOOMED TO FAIL in patients with non-mutated tumors – Low TMB?

Don’t give up on low TMB Patients – Shared Cancer Antigens

Human Cancer Biology

The Prioritization of Cancer Antigens: A National Cancer Institute Pilot Project for the Acceleration of Translational Research

Martin A. Cheever,[1] James P. Allison,[2] Andrea S. Ferris,[3] Olivera J. Finn,[4] Benjamin M. Hastings,[3] Toby T. Hecht,[5] Ira Mellman,[7] Sheila A. Prindiville,[6] Jaye L. Viner,[6] Louis M. Weiner,[8] and Lynn M. Matrisian[6]

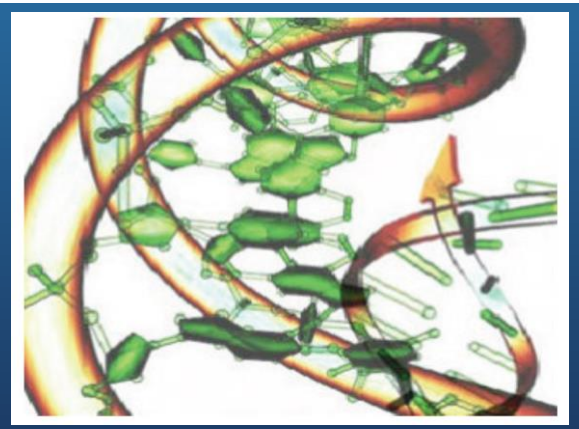
Clin Cancer Res 2009;15:5323-5337

NIH

THE CANCER GENOME ATLAS

National Cancer Institute

National Human Genome Research Institute



- Identifies genes in cancer that are upregulated, amplified, mutated compared to normal tissue
- Associations with survival

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Cancer Vaccines As Single Agents: Success at Prevention – HBV, HPV

NIH NATIONAL CANCER INSTITUTE

Trials found the vaccines provide nearly 100% protection against persistent cervical infections with HPV types 16 and 18 and the cervical cell changes that these persistent infections can cause.

https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet

Neonatal HBV vaccination or catch-up vaccination at young ages reduces HCC incidence by 90% in young adults.

PLoS Med 11 (12): e1001774, 2014.

The Future…
We will see more vaccines to prevent cancer!

- High risk of colon cancer (MUC1)
- Breast cancer for BRCA ½ + other
- Oral dysplasia – HNSCC
- Others..

Cancer Vaccines As Single Agents: Fail as Therapy for Advanced Cancer

Nat Med; September 01, 2004

In our cancer vaccine trials of 440 patients, the objective response rate was low (2.6%), and comparable to the results obtained by others".

Cancer Vaccines As Single Agents: Fail as Therapy for Advanced Cancer

nature medicine

Perspective | Published: 01 September 2004

Cancer immunotherapy: moving beyond current vaccines

Steven A Rosenberg ✉, James C Yang & Nicholas P Restifo

Nat Med; September 01, 2004

Clinical Cancer Research

Is the "3+3" Dose-Escalation Phase I Clinical Trial Design Suitable for Therapeutic Cancer Vaccine Development? A Recommendation for Alternative Design

Osama E. Rahma[1,2], Emily Gammoh[1], Richard M. Simon[3], and Samir N. Khleif[1,4]

Clin Cancer Res; 20(18) September 15, 2014

In our cancer vaccine trials of 440 patients, the objective response rate was low (2.6%), and comparable to the results obtained by others".

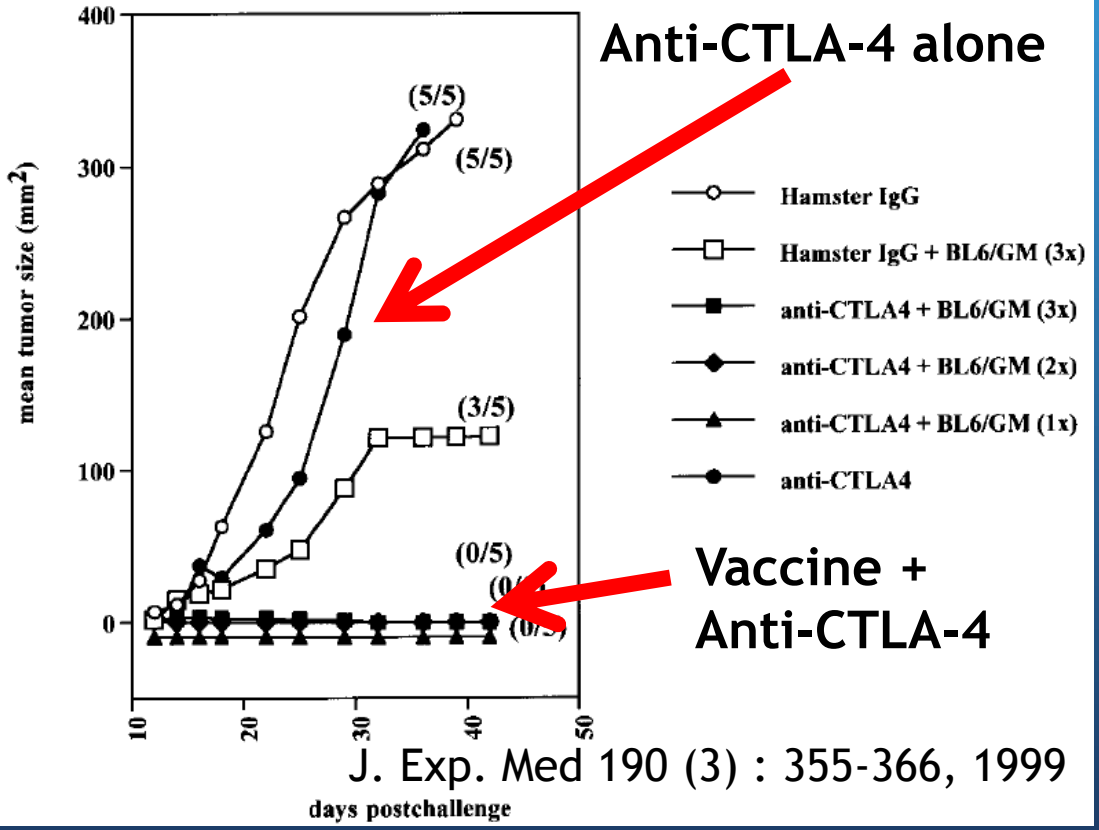
While ineffective: Vaccines are safe – 239 Ph1 trials : Gr 3/4 SAE were 2/1000 vaccines.

IMPORTANT FOR USE IN COMBO I-O

Vaccines in Combination with I-O Often More Therapeutic

Combination Immunotherapy of B16 Melanoma Using Anti–Cytotoxic T Lymphocyte–associated Antigen 4 (CTLA-4) and Granulocyte/Macrophage Colony-Stimulating Factor (GM-CSF)-producing Vaccines Induces Rejection of Subcutaneous and Metastatic Tumors Accompanied by Autoimmune Depigmentation

By Andrea van Elsas, Arthur A. Hurwitz, and James P. Allison



J. Exp. Med 190 (3) : 355-366, 1999

While showing this for vaccine, this same strategy can be effective with other strategies.

- Chemo/Rad
- Antibodies
- BiTEs / DARTs
- Oncolytic viruses

FUTURE: Cancer Vaccines + Other Immunotherapy: Hold Promise

January 2019

Combining Immune Checkpoint Blockade and Tumor-Specific Vaccine for Patients With Incurable Human Papillomavirus 16–Related Cancer

A Phase 2 Clinical Trial

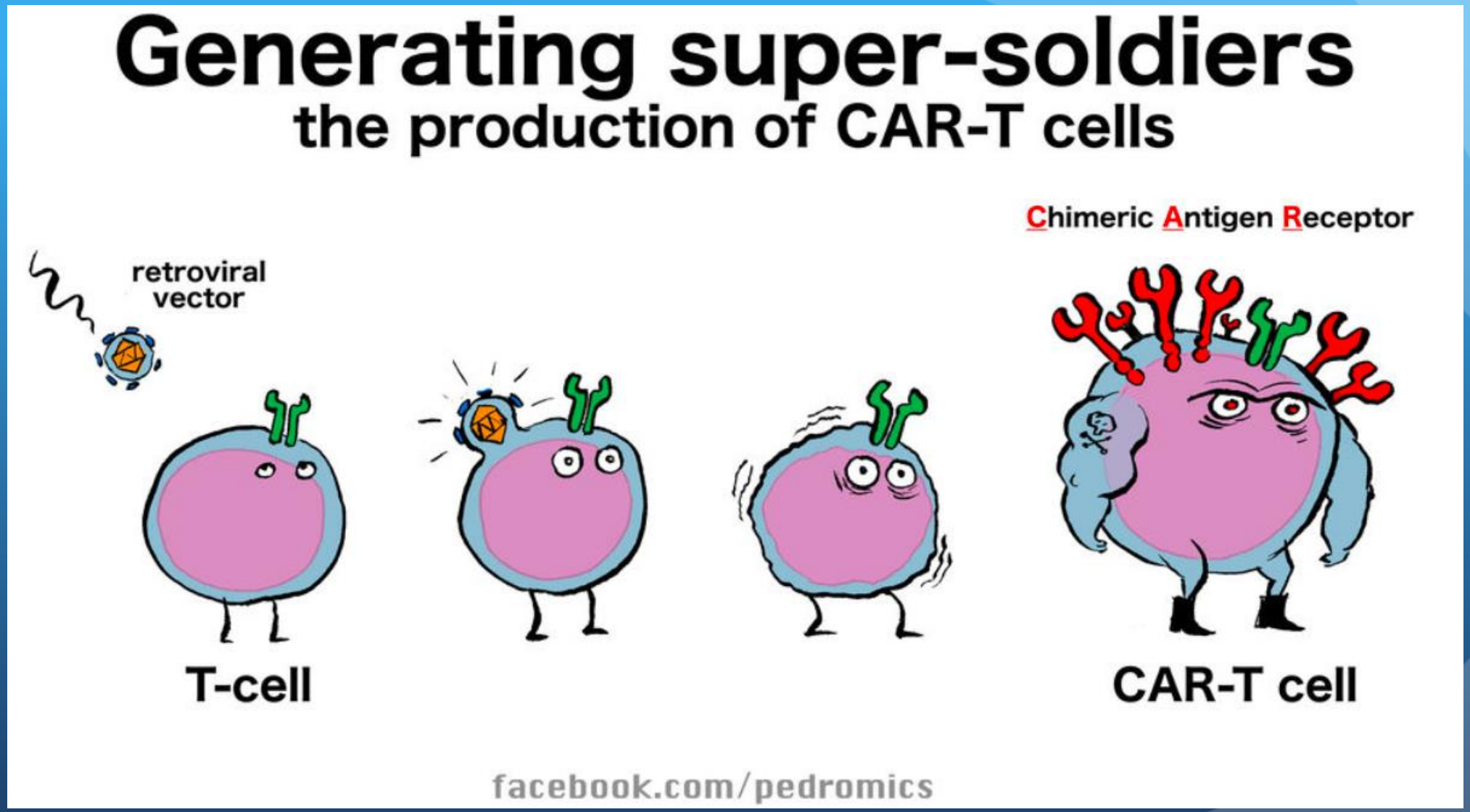
Erminia Massarelli, MD[1]; William William, MD[2]; Faye Johnson, MD, PhD[2]; Merrill Kies, MD[2]; Renata Ferrarotto, MD[2]; Ming Guo, MD[3]; Lei Feng, MS[4]; J. Jack Lee, PhD[4]; Hai Tran, PharmD[2]; Young Uk Kim, PhD[5]; Cara Haymaker, PhD[6]; Chantale Bernatchez, PhD[5]; Michael Curran, PhD[7]; Tomas Zecchini Barrese, MD[6]; Jaime Rodriguez Canales, MD[6]; Ignacio Wistuba, MD[6]; Lerong Li, MS[8]; Jing Wang, PhD[8]; Sjoerd H. van der Burg, PhD[9]; Cornelis J. Melief, PhD[10,11]; Bonnie Glisson, MD[2]

EARLY DATA: The overall response rate of 33% and median overall survival of 17.5 months is promising compared with PD-1 inhibition alone in similar patients.
A randomized clinical trial is warranted

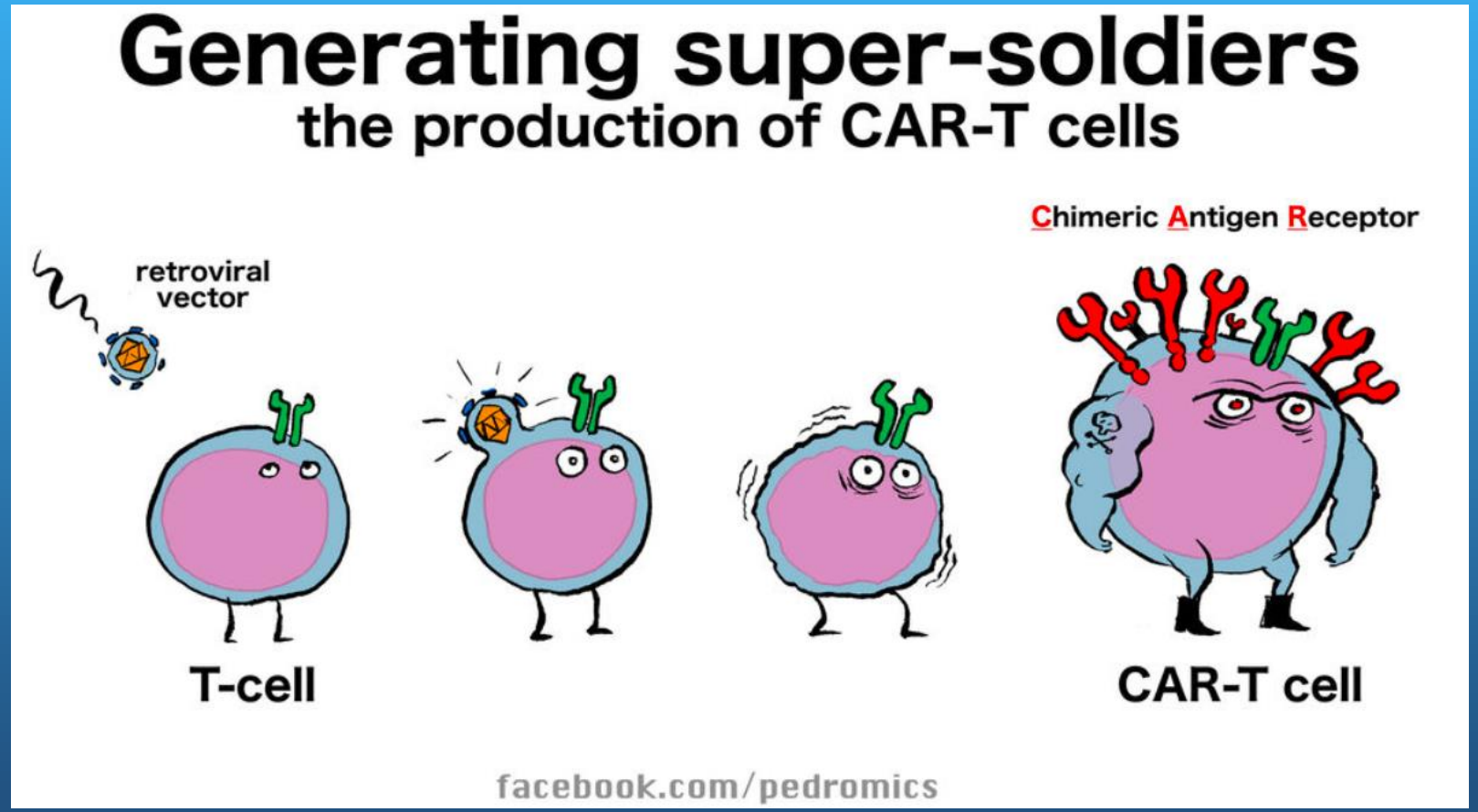
JAMA Oncol. 2019;5(1):67-73.

EARLE A. CHILES RESEARCH INSTITUTE

T Cell Adoptive Transfer



FUTURE: T Cell Adoptive Transfer



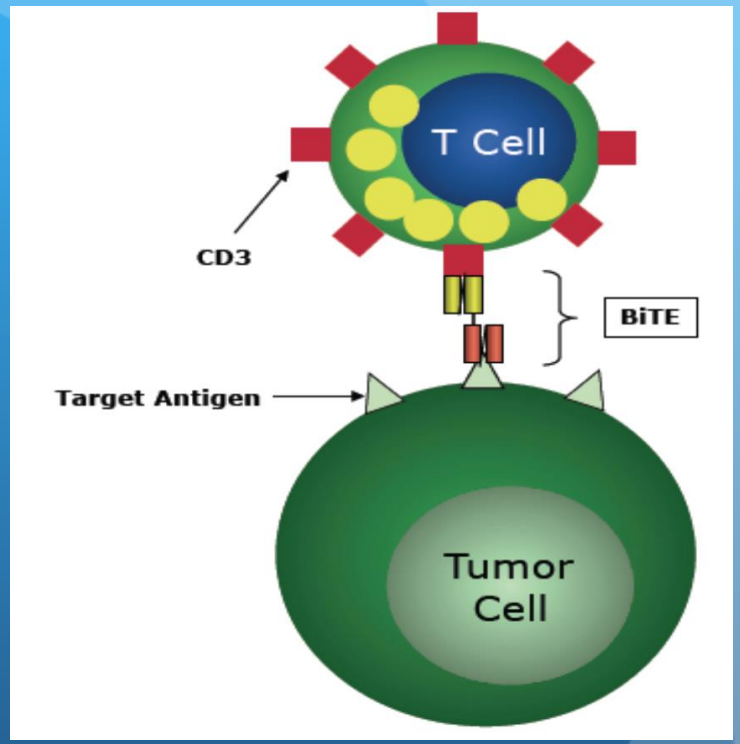
TCR, CAR T/NK & TIL -

These will continue to show improved therapeutic activity:

- Resistance to suppression (TGF-b)
- Improved tumor infiltration
- Better persistence / memory (TEM and CM) – VST
- Reduced price - as fewer cells will be needed

FUTURE: Redirected T Cells

- Bi-specifics / BiTEs / DARTs
  - Target T cells to tumor
  - Activate the T cells



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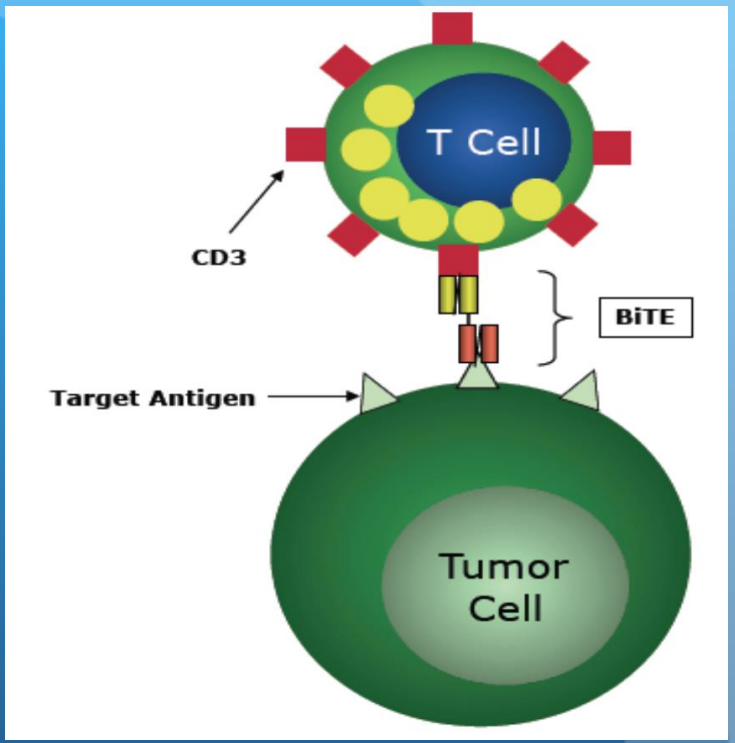
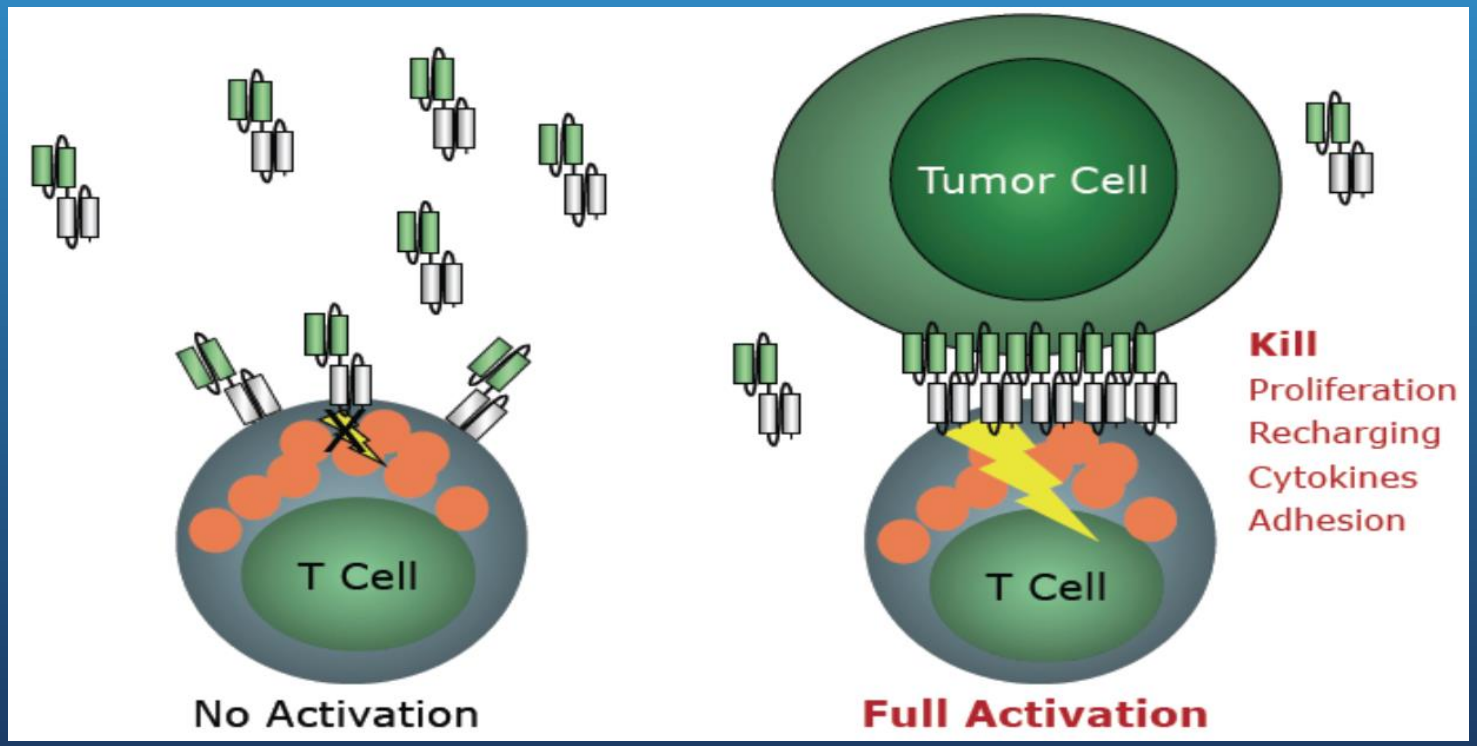


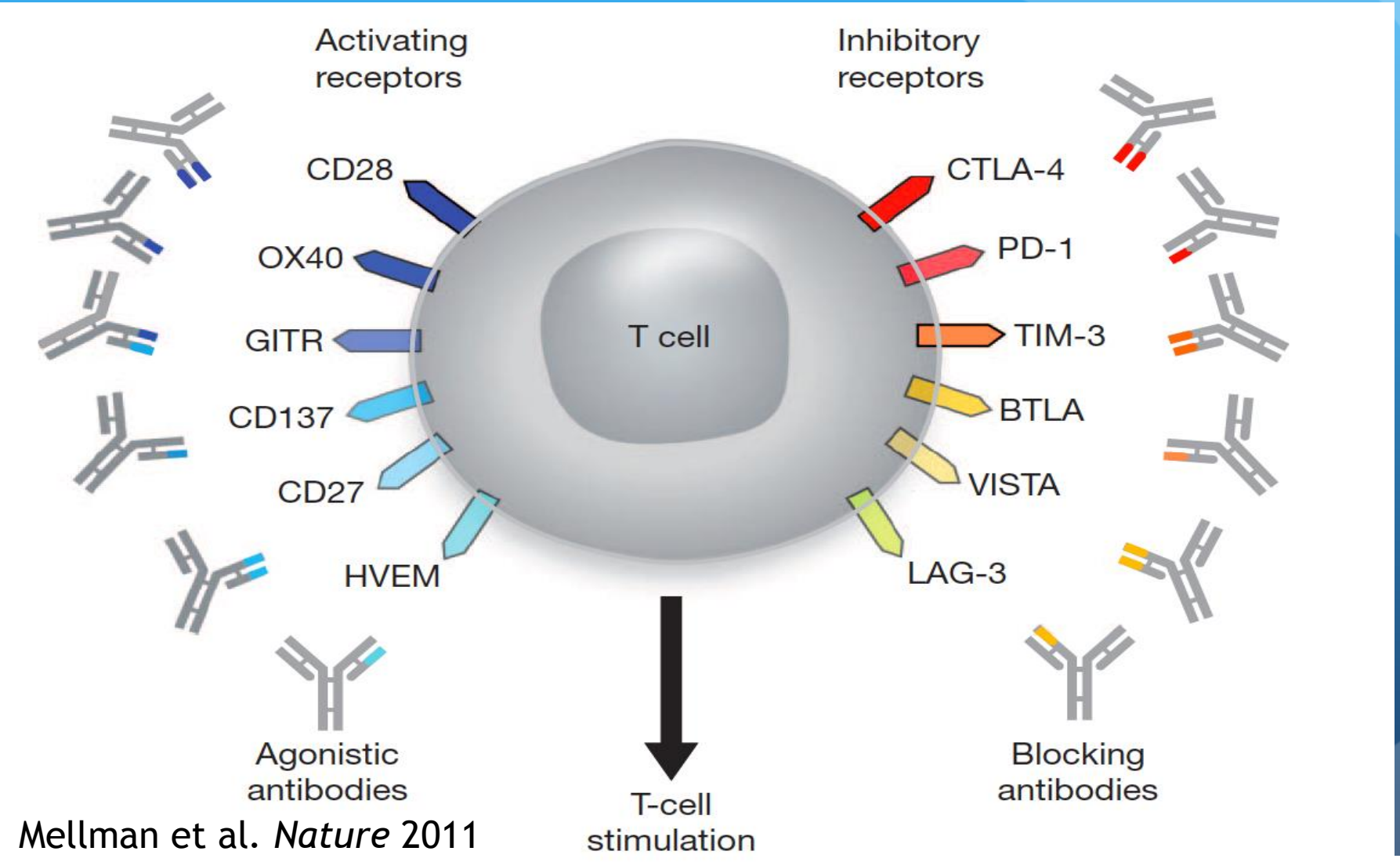


FUTURE: Redirected T Cells

Bi-specifics / BiTEs / DARTs that activate and target T cells to tumor

- These will show striking results in some histologies as combinations of these are administered for multiple Ags and with “supportive” I-O combos.
- Expect Antibody-Drug Conjugates – Targeting drug to tumor will also be used in combination with other I-O agents

Activating Receptors / Costimulatory Molecules



Mellman et al. *Nature* 2011

Clinical Trials of T cell Agonists: Advanced Cancer

- As single agents – Disappointing
- In combination with PD-1/PD-L1 –
  - some are showing activity

Clinical Trials of T cell Agonists: Advanced Cancer

- As single agents – Disappointing
- In combination with PD-1/PD-L1 –
  - some are showing activity

The Problem: Did the agonists that didn't exhibit therapeutic efficacy have an effect on anti-cancer immunity?

Another Problem:

In 2019 the field is unsure of….

- The mechanism of “Complete” tumor rejection?

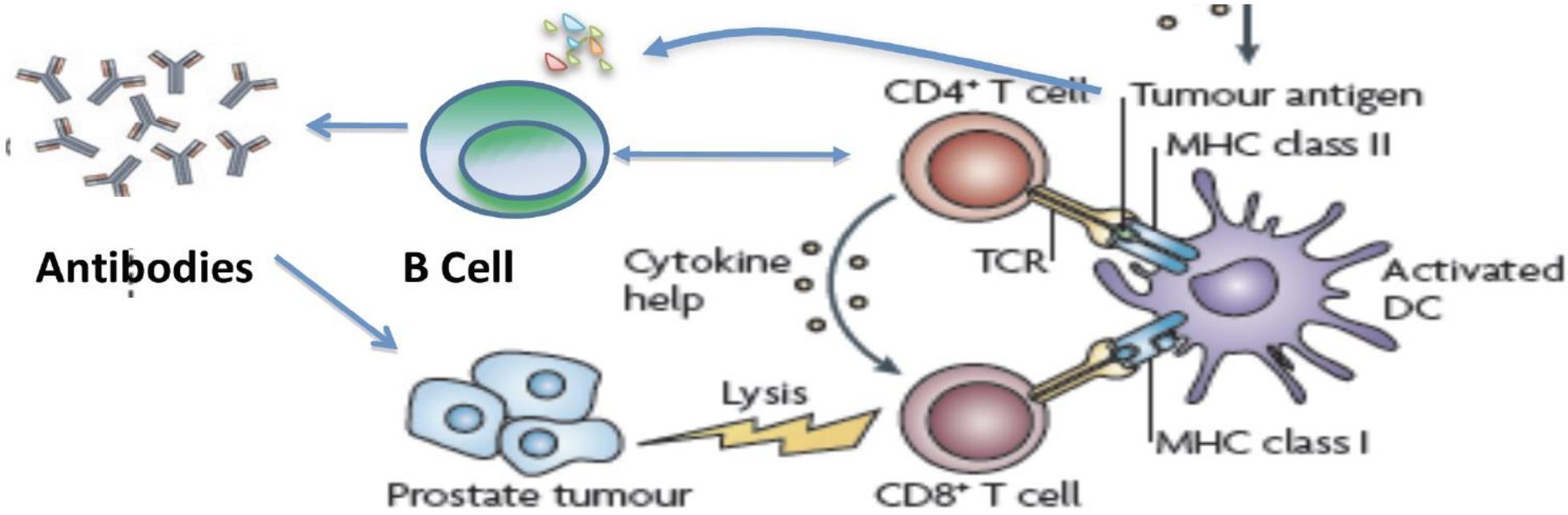
- If T cell mediated – What is the antigen(s)
  - Historically TAA (gp100, MAGE, TRP)
  - **Current focus on neoantigens**

But what about all the other possible TAAs?

What about other effector mechanisms?

http://gravasco.blogspot.com/

Immunosurveilance: Coordinated B and T cell Response to Cancer



Modified from
Drake. et al, Nat Rev Immunol. 2010 10(8)
Goodnow et al, Nature Immunology. 10(11)

Coordinated IgG and CD8 T cell Response
Kwek SS, et al, J. Immunol 2012
Tripathi SC et al, PNAS 2016
Hulett et al, J. ImmunoTherapy Cancer 2018

SHORT REPORT Open Access

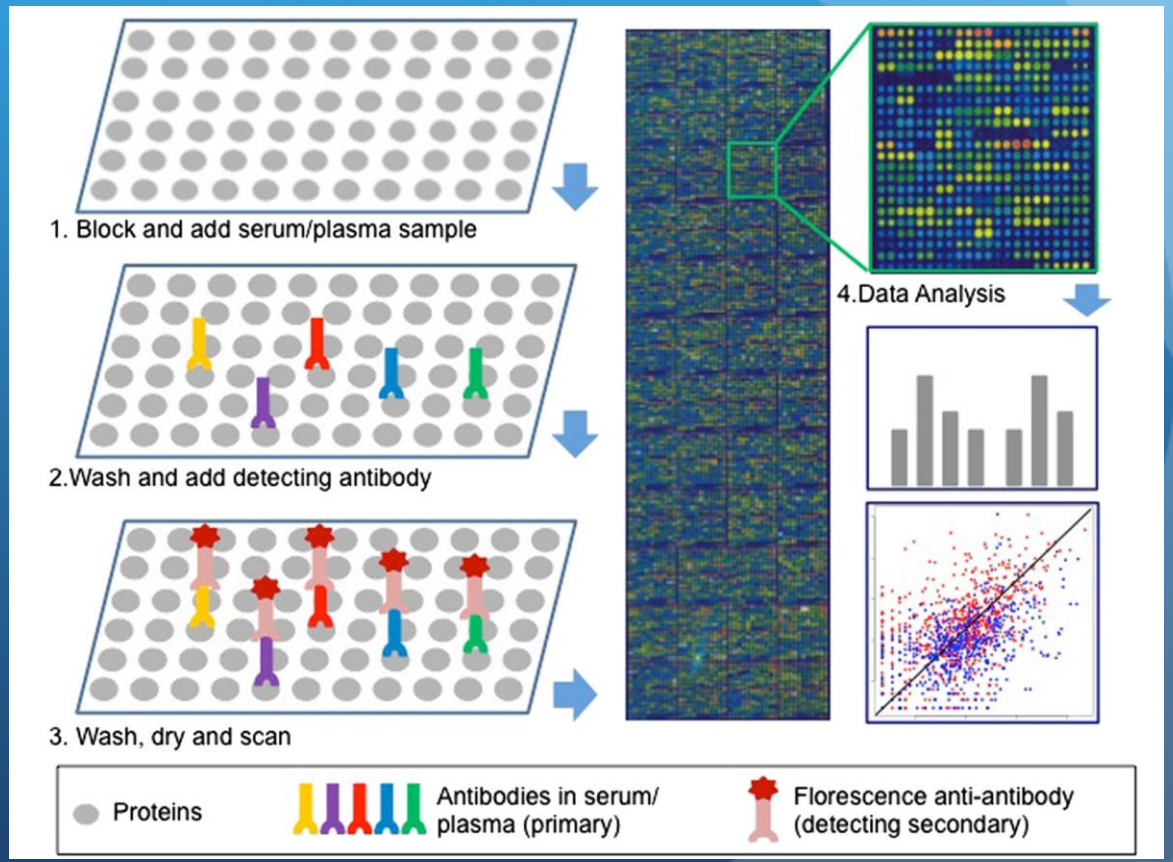
Immune Monitoring Technology Primer: protein microarray ('seromics')

Jianda Yuan[1*], Ena Wang[2] and Bernard A. Fox[3]

Yuan *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:2

Method for Identifying the development or augmentation of Ab responses against human Proteins

- CDI HuProt
  19,000 proteins
- Invivogen ProtoArray
  9,000 proteins
- MAP
  5,000 proteins



Based on Ab Response Can Identify Target of T Cells

- TCR technologies can track T cell clones (PBL/Tu)
- This will be used to assess response to combination I-O

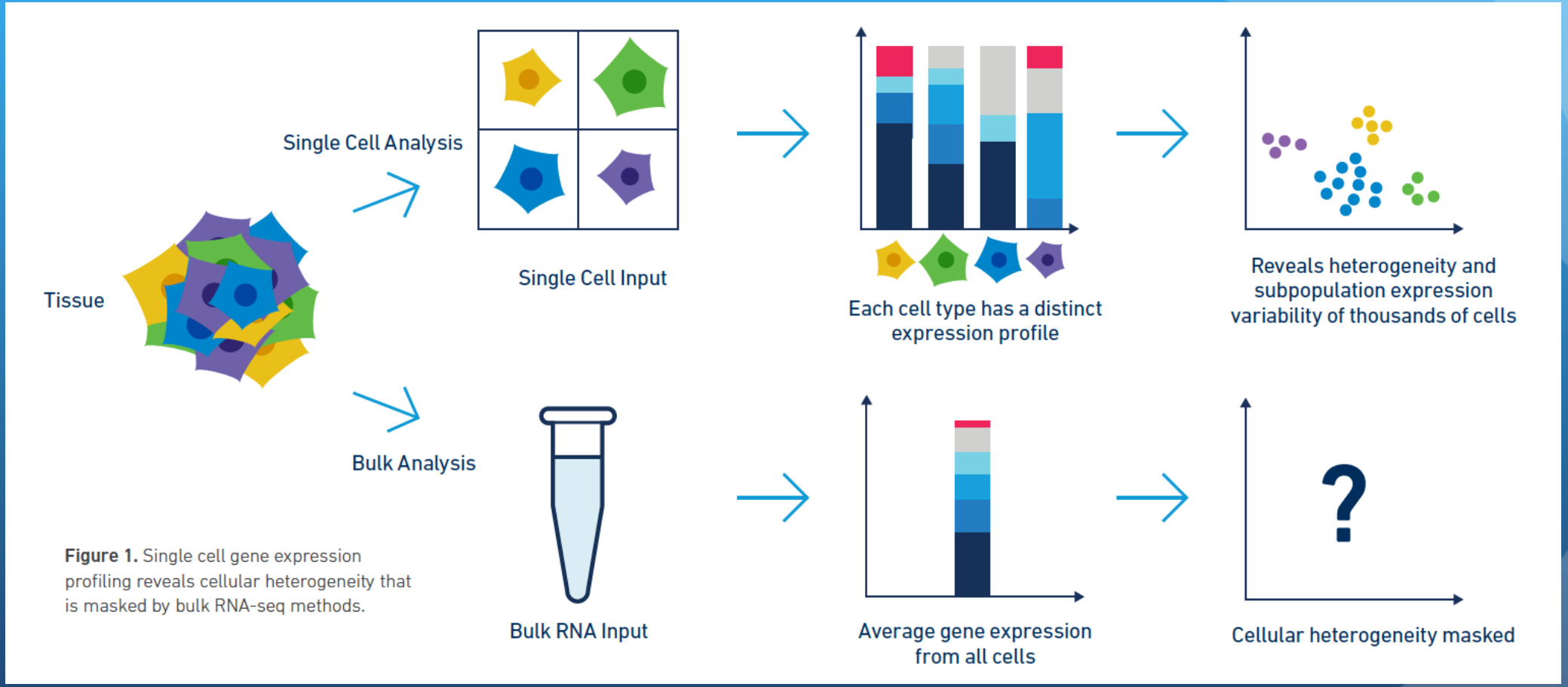


Figure 1. Single cell gene expression profiling reveals cellular heterogeneity that is masked by bulk RNA-seq methods.

https://support.10xgenomics.com/single-cell-gene-expression/

Checkpoint Blockade
Car Analogy: Taking the brake off

Checkpoint blockade
Anti-PD-1/PD-L1
Anti-CTLA-4

FUTURE: Combine All Three (or more)

Ignite & Steer

Chemotherapy
Radiation
Bi-specifics
Intra-Tu Tx
Vaccines

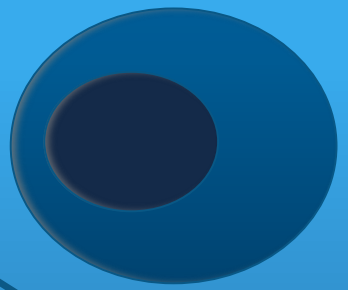
Gas

T Cell Agonists
OX40, GITR, …
IL-2 / IL-7 / IL-15

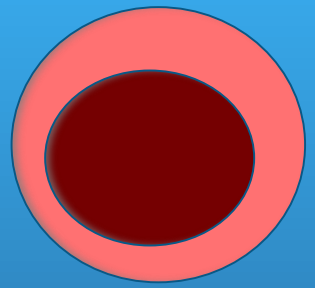
Brake

Checkpoint blockade
Suppressors
TIGIT

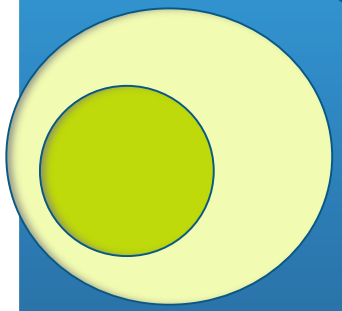
Induce Spectrum of anticancer immunity



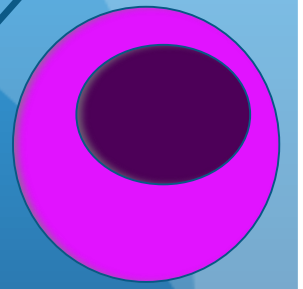
CD8 – CTL
Class I restricted
Cytotoxicity
Cytokines



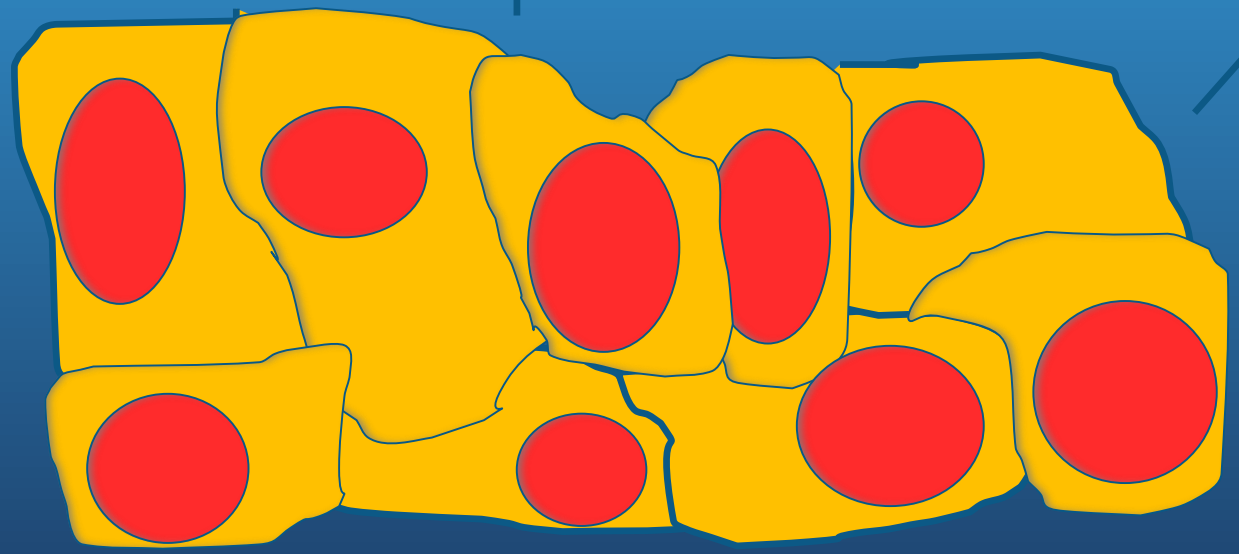
CD4 – Help
Class II restricted
Cytokines
Cytotoxicity



B cells – Ab to
Membrane proteins
ADCC & CDC
Possibly effective against HLA & B2M loss



NK cells
Cytotoxicity
Cytokines
effective against HLA & B2M loss



Tumor Cells

Body Weight Affects Cancer Risk

- Being overweight or obese is clearly linked to an overall increased risk of cancer.
  - 8% of all cancers in the United States-
  - 7% of all cancer deaths.

Clearly linked with an increased risk of:

- Breast (in women past menopause)
- Colon and rectum
- Endometrium (lining of the uterus)
- Esophagus
- Kidney
- Pancreas

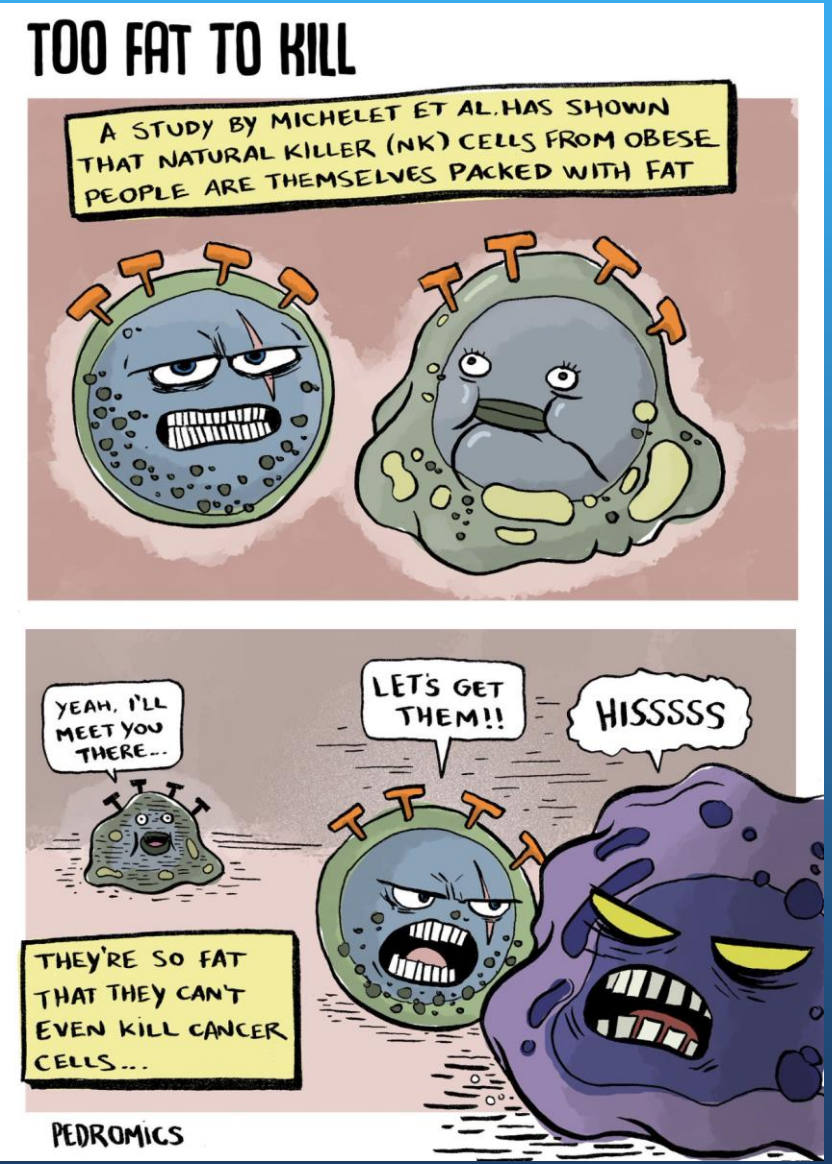
May raise the risk of:

- Gallbladder
- Liver
- Non-Hodgkin lymphoma
- Multiple myeloma
- Cervix
- Ovary
- Aggressive prostate cancer

https://www.cancer.org/cancer/cancer-causes/diet-physical-activity/body-weight-and-cancer-risk/effects.html

Earle A. Chiles Research Institute

How might body weight affect cancer risk?



Immune system function and inflammation:

- Reduced NK Function

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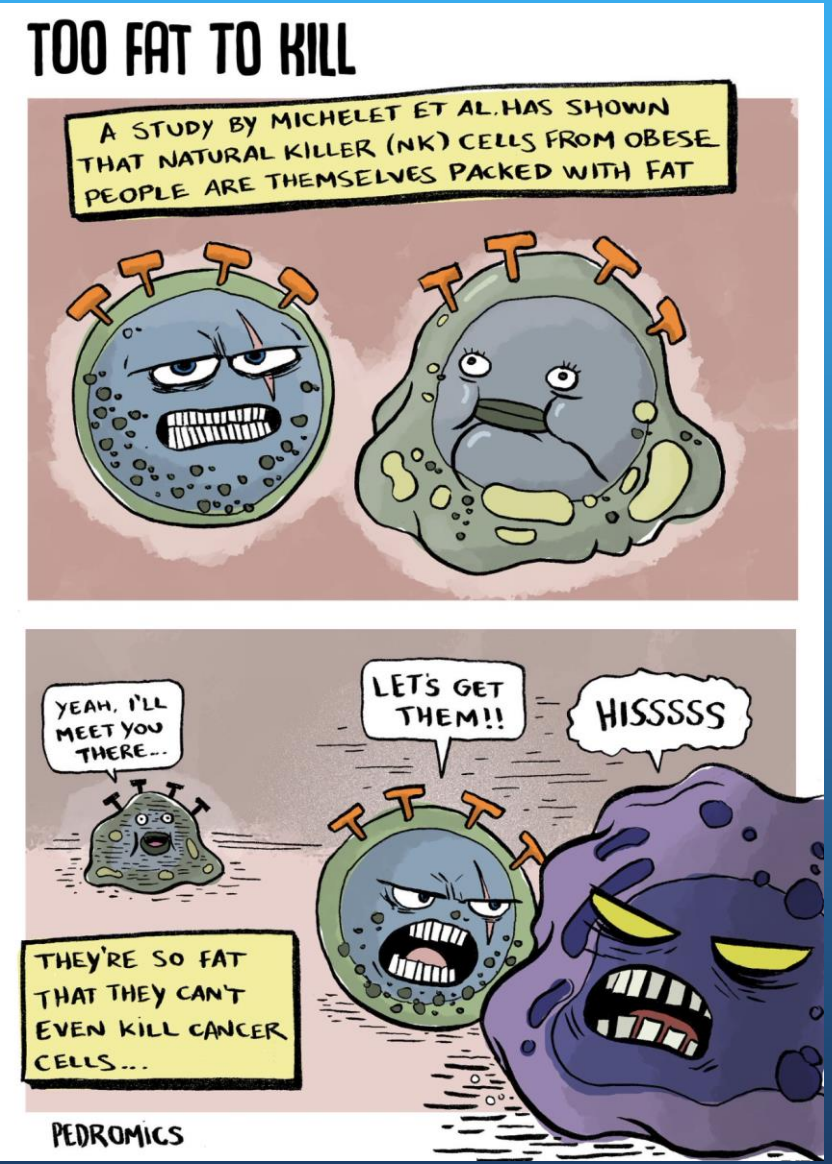
How might body weight affect cancer risk?



Immune system function and inflammation:

- Reduced NK Function

FUTURE: Metabolic reprogramming of NK cells may improve cancer outcomes in obesity

Metabolic reprogramming of natural killer cells in obesity limits antitumor responses

Xavier Michelet, Lydia Dyck, Andrew Hogan, Roisin M. Loftus, Danielle Duquette, Kevin Wei, Semir Beyaz, Ali Tavakkoli, Cathriona Foley, Raymond Donnelly, Cliona O'Farrelly, Mathilde Raverdeau, Ashley Vernon, William Pettee, Donal O'Shea, Barbara S. Nikolajczyk, Kingston H. G. Mills, Michael B. Brenner, David Finlay & Lydia Lynch

Nature Immunology **19**, 2018

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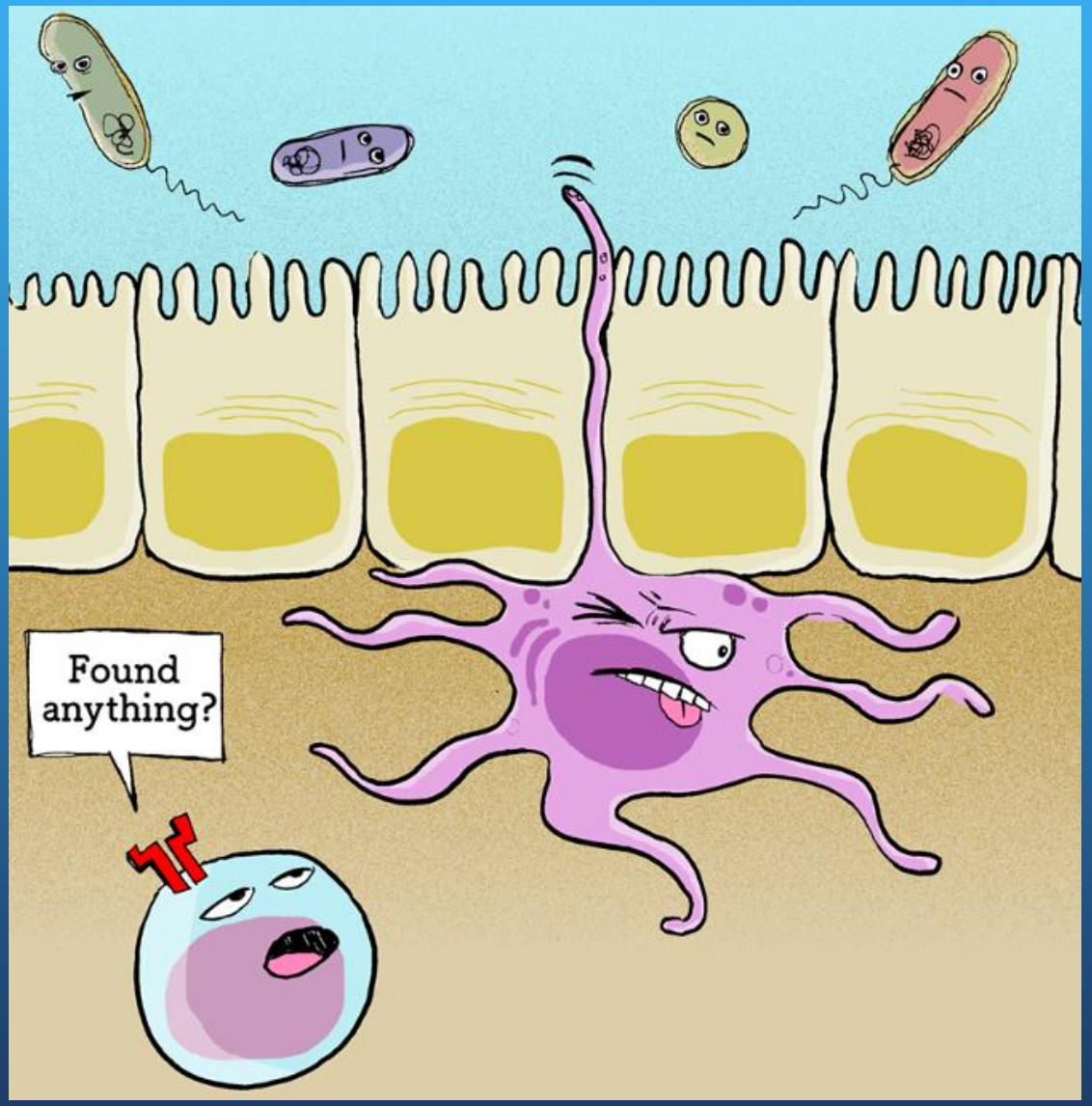
Microbiome Effects on Immune Responsiveness



Clinical Trials.

Fecal Transplants from Super responders.

FUTURE: Bacteria, bacteriophages used in combo I-O studies

Objectives: FDA Workshop on Immune-Oncology Combos

1. To identify best practices regarding patient selection for immune-oncology combinations –*Multiplex/TMB/GEP/PD-L1*
2. To identify best practices regarding dose selection and optimization for IO combinations – *Data to suggest schedule may be important*
3. To discuss the utility of biomarkers as pharmacodynamics endpoints to aid in dose optimization.
4. To discuss how the expectation of the demonstration of the contribution of each agent has to a combination and strategies to isolate the effect of each individual agent –

https://www.fda.gov/Drugs/NewsEvents/ucm562746.htm

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